

## The Prevalence of Valvular and Vascular Calcifications in Prevalent Hemodialysis Patients

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### ABSTRACT

**Background:** Patients with chronic kidney disease (CKD) are likely to get valve calcification 10-20 years earlier than the normal population secondary to uremia. This condition is typically diagnosed through transthoracic echocardiography. Vascular calcification resulted in arterial stiffness and an increase in pulse wave velocity (PWV) in large elastic-type arteries. The intima-media complex acts as a stand-in marker for atherosclerosis and is where lipids are deposited during plaque development. **Objective:** This study aimed to estimate the prevalence of valvular and vascular calcifications in hemodialysis patients at Ain Shams Specialized Hospital, Cairo, Egypt. **Patients and Methods:** A cross-sectional pilot study was conducted on 100 prevalent hemodialysis patients who were maintained on thrice-weekly hemodialysis sessions at Ain Shams Specialized Hospital in the period from January to June 2020. Echocardiography was performed to assess the presence of valvular calcification; PWV was measured to evaluate vascular stiffness. Intima-media thickness (IMT) and carotid plaques were detected using an echo-doppler study of the carotid arteries. **Results:** The study was conducted on 100 patients undergoing hemodialysis treatment for 6 months. Out of these, 55% of patients were males. Among the studied patients, 15% had mitral valve (MV) calcification, 61% had aortic valve (AV) calcification, and 17% had carotid plaques. Patients with calcification of the MV had an aortic PWV mean of 1.587 m/s. 53.33% of these patients had carotid plaques and the IMT mean was 6.567mm higher than the non-MV calcification group. Patients with aortic AV calcifications had a mean IMT of 5.038 mm and a higher percentage (22.95%) of carotid plaques compared to the non-aortic calcification group. Patients with carotid plaques had higher levels of aortic wave pulse velocity (mean 1.54 m/s) and IMT (mean 7.653mm). Also, there was a significant positive correlation between intimal medial thickness and aortic PWV (p-value= 0.003), and a significant negative correlation between IMT and ejection fraction (p-value=0.048\*). **Conclusions:** Valvular calcification is widespread in individuals on hemodialysis, with AV calcification being more common than MV calcification. Hemodialysis patients with valvular calcifications had a higher incidence of carotid intimal thickness. Aortic wave pulse velocity correlated with increasing carotid intimal thickness and predicted arterial atherosclerosis.

**Keywords:** IMT, PWV, CKD, Hemodialysis, MV calcification, AV calcification.

### INTRODUCTION

CKD is the primary cause of death for hemodialysis patients, with mortality rates three to thirty times greater than in the general population. Peripheral vascular disease, ischemic cardiomyopathy, myocardial infarction, and stroke are the most frequent causes of these fatalities<sup>(1)</sup>.

Vascular calcification, or the abnormal buildup of calcium salts in the vascular tissue, including the heart, blood arteries, and valves, is a major risk factor for cardiovascular death in individuals with end-stage renal disease (ESRD). There might be calcifications of the vasculature in both the medial and intimal layers. However, in ESRD, medial calcification is thought to be the more prevalent and significant kind of calcification<sup>(2)</sup>.

The process of vascular calcification causes arteries to become stiffer, which raises the PWV in big elastic-type arteries. This is brought about by alterations in the inherent characteristics of the arterial wall, which eventually have an impact on the artery's structure. This process, which can lead to anomalies in the arterial anatomy such as thickening of the intima, increased extracellular matrix, and widespread calcification, can be made worse in individuals with CKD by uremia<sup>(3)</sup>.

According to recent research, the AV leaflets' internal active cellular process is thought to be what is

behind AV calcification formation similar to those found in atherosclerosis, including lipoprotein accumulation, persistent inflammation, and active leaflet calcification. AV calcification is a symptom of systemic atherosclerosis, as evidenced by a prior population-based investigation that found it to be linked to a high prevalence of atherosclerotic risk factors<sup>(4)</sup>. A number of imaging modalities, including echocardiography, cardiac CT, plain radiography, and ultrasonography, have been used to assess the degree of vascular and valvular calcification<sup>(5)</sup>. Vascular stiffness is measured using PWV. The conduction velocity of the pulse rises throughout the vessel length when the blood vessels become less elastic. Reduced elasticity can be caused by a number of conditions, including atherosclerosis, calcification of the vascular wall, and alterations in the amount of collagen and elastin in the vessel wall<sup>(6)</sup>.

The reduced capacity of an artery to expand and contract in response to variations in pressure is referred to as arterial stiffness. Vessel stiffness is measured by two parameters: distensibility and compliance. PWV, or the pace at which the pressure pulse spreads across the arterial tree, rises in the presence of decreased compliance/distensibility. The relationship between PWV and relative arterial compliance and arterial distensibility is inverse<sup>(7)</sup>. Hemodialysis patients have decreased collagen and

other extracellular matrix proteins' flexibility and digestibility as a result of an increase in reactive carbonyl chemicals such as methylglyoxal. In reaction to the increased stress brought on by hypertension, this may cause the artery walls to thicken. Diffuse calcifications in the arterial medium, which cause a histological appearance distinct from calcifications in complicated atherosclerotic plaque and occur with little to no inflammation, are also responsible for arterial stiffness in individuals with CKD <sup>(7)</sup>. Echocardiography is an easy, repeatable, non-invasive, and reasonably priced way to test for calcific valve disease, according to the KDIGO recommendations. Despite the fact that several researches have demonstrated the link between valve calcification and death, there are still some disagreements on this issue <sup>(8)</sup>. Our study aimed to estimate the prevalence of valvular and vascular calcifications in hemodialysis patients at Ain Shams Specialized Hospital.

## PATIENTS AND METHODS

A cross-sectional pilot study was conducted on 100 prevalent hemodialysis patients who were maintained on thrice-weekly hemodialysis sessions, four hours each in Ain Shams University Hemodialysis Unit in the period from January to June 2020.

**Inclusion criteria:** Patients aged 18 years and above, who have undergone hemodialysis for more than 6 months, and had a stable clinical condition without cardiovascular complications.

**Exclusion criteria:** Patients over 60 years old, and patients with infection, inflammation, malignancy, uncontrolled hypertension, or diabetes.

Demographic data, including age and sex, and medical history, including the cause of ESRD and dialysis vintage, were collected from the patient's files and recorded.

**Study design:** All patients underwent four-hour hemodialysis sessions using bicarbonate dialysate solutions, which had the following composition: Na<sup>+</sup> 140 mmol/l, Cl<sup>-</sup> 111 mmol/l, Ca<sup>2+</sup> 1.5 mmol/l, Mg<sup>2+</sup> 0.5 mmol/l, K<sup>+</sup> 2 mmol/l, acetate 2 mmol/l, and bicarbonate 33 mmol/l. During the session, the average blood flow was 300–350 ml/min, and the dialysate flow was 500–800 ml/min with a target dialysis dose of (Kt/V) > 1.2. Unfractionated heparin was used as an anticoagulant. All patients received high-flux hemodialysis using the FX80 polysulfone membrane (Fresenius Medical Care in Germany). The membrane had a surface area of 1.8 m<sup>2</sup>, an ultrafiltration coefficient of 59 ml/h x mmHg, and a urea clearance of 276 ml/min at a blood flow rate of 300 ml/min. The ultrafiltration goal was determined based on interdialytic weight gain.

**Biochemical measures** included complete blood count, magnesium, sodium, potassium, calcium, phosphorus, calcium phosphorus (Ca/PO<sub>4</sub>) product, parathyroid hormone, and lipid profile (total

cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) using standard laboratory techniques.

**Carotid IMT** measurement using the echo-Doppler study of carotid arteries with stressing on the presence of carotid plaques through ultrasonographic examination of the carotid artery using General Electric Divid 9 using a duplex probe (11 L)

**Transthoracic echocardiography** was done for all patients using a General Electric Divid 9 (General Electric, Boston, Massachusetts, US) 2.5 MHZ transducer probe with stressing on ejection fraction, valve calcification (VC), and left ventricular mass, mass index, and PWV, which is computed by dividing the pulse wave's distance by the time it takes to traverse that distance, demonstrating segmental artery elasticity.

**Ethical approval:** Ain Shams Faculty of Medicine Ethics Committee approved this study ((Approved No.: FWA 000017585)). After obtaining the necessary information, all participants provided signed consent. The Helsinki Declaration was observed throughout the study's conduct.

## Statistical analysis

SPSS Version 20.0 computer was used to do statistical analysis. According to the kind of data collected for each parameter, appropriate analysis was done once the data was provided. As well as the frequency and proportion of non-numerical data, parametric numerical data's mean, standard deviation, and range are provided. In order to determine whether the data followed a parametric or non-parametric distribution, the Shapiro-Wilk test was performed to examine the normality of the data. A parametric variable's difference between two independent means of two research groups was evaluated for statistical significance using the independent sample t-test. The link between two qualitative variables was investigated using the X<sup>2</sup> test. Fisher's Exact test was utilized when the predicted count was less than 5 in more than 20% of the cells. The coefficient of correlation between Spearman's d (The degree to which two quantitative variables have a linear link) was gauged using correlation. There is a range of values for the correlation coefficient, r, from +1 to -1. The absence of any correlation between the two variables was shown by a value of 0. A positive association was shown by a number larger than 0, meaning that the value of one variable rises in proportion to the value of the other. When one variable's value rises, the other variable's value falls, indicating a negative relationship with a value smaller than 0. When it is equal to or less than 0.05, a significant p-value is taken into account.

## RESULTS

The study involved 100 patients who were receiving hemodialysis treatment with a mean duration of 7.530 years. The mean age of the studied group was 40.640 ± 14.511 years (Table 1).

**Table (1):** Baseline characteristics of the studied population

		Number	Percentage %
	<b>Males</b>	55	55
<b>Sex</b>	<b>Females</b>	45	45
<b>Virology (HCV)</b>	<b>Negative</b>	72	72
	<b>Positive</b>	28	28
<b>Vascular access</b>	<b>AVF</b>	94	94
	<b>Permicath</b>	6	6
<b>Etiology of ESRD</b>			
	Hypertension	30	30.00
	Diabetes	23	23.00
	Obstructive uropathy	11	11.00
	Analgesic abuser	10	10.00
	Glomerulonephritis	9	9.00
	Congenital disease	5	5.00
	ADPKD	3	3.00
	Systemic lupus nephritis	3	3.00
	Postpartum ATN	2	2.00
	Preeclampsia	2	2.00
	Amyloidosis	1	1.00
	Alport	1	1.00

Table (2) showed that the mean EF was 61.281 in the studied population, with a mean carotid IMT of 4.456 mm and a mean aortic wave pulse velocity of 1.394 m/s. Among the patients, 15% had MV calcification, 61% had AV calcification, and 17% had carotid plaques.

**Table (2):** Descriptive analysis of Laboratory data, echocardiography findings, and carotid duplex findings of the studied population

<b>Descriptive Statistics</b>			
		<b>Mean ± SD</b>	
<b>Ca (mg/dl)</b>		8.563±0.895	
<b>Ca/po4 product</b>		38.231 ± 9.42	
<b>Po4 (mg/dl)</b>		4.482 ± 1.04	
<b>Intact PTH (pg/ml)</b>		580.370 ± 13.67	
<b>Hb (gm/dl)</b>		9.857 ± 1.597	
<b>Na (mEq/l)</b>		136.180 ± 3.647	
<b>K(mEq/l)</b>		5.194 ± 0.767	
<b>Mg</b>		2.074 ± 0.256	
<b>TGs (mg/dl)</b>		118.370 ± 18.352	
<b>LDL (mg/dl)</b>		108.849 ± 26.88	
<b>HDL (mg/dl)</b>		43.478 ± 9.988	
<b>Cholesterol (mg/dl)</b>		177.600 ± 43.709	
<b>EF (ejection fraction) %</b>		61.281 ± 7.930	
<b>Aortic wave pulse velocity (m/s)</b>		1.39 ± 0.268	
<b>Carotid IMT (mm)</b>		4.456 ± 1.011	
<b>Echocardiographic findings</b>		<b>No.</b>	<b>%</b>
<b>MV (Mitral valve) calcification</b>	<b>Present</b>	15	15%
	<b>Absent</b>	85	85%
<b>AV (Aortic valve) calcification</b>	<b>Present</b>	61	61%
	<b>Absent</b>	39	39%
<b>TV (Tricuspid valve) calcification</b>	<b>Present</b>	0	0%
	<b>Absent</b>	100	100%
<b>Carotid Plaques</b>	<b>Absent</b>	83	83%
	<b>Present</b>	17	17%

According to Table (3), the two groups differed significantly in terms of aortic PWV (p = 0.002\*), plaque presence (p < 0.001\*), and IMT (p < 0.001\*). There were no significant differences between the groups in terms of age, length of hemodialysis, and laboratory data.

**Table (3):** Comparison between patients without MV calcifications and with MV calcifications as regards age, duration of hemodialysis, laboratory data, echocardiography, and carotid duplex findings

	MV calcification						T-Test		
	Without MV calcification 85 patients			With MV calcification 15 patients			T	P-value	
	Mean	±	SD	Mean	±	SD			
Age (years)	39.635	±	14.361	46.333	±	14.519	-1.663	0.100	
Duration of HD (years)	7.388	±	5.817	8.333	±	6.597	-0.569	0.571	
Ca (mg/dl)	8.556	±	0.902	8.600	±	0.879	-0.173	0.863	
Ca/po4 product	38.545	±	9.432	36.452	±	1.732	0.511	0.610	
Po4 (mg/dl)	4.527	±	1.081	4.227	±	1.319	0.641	0.523	
PTH (pg/ml)	602.012	±	145.953	457.733	±	84.173	1.024	0.308	
Hb (g/dl)	9.848	±	1.576	9.907	±	1.768	-0.130	0.897	
Na (mEq/L)	136.165	±	3.804	136.267	±	2.685	-0.099	0.921	
K (mEq/L)	5.228	±	0.800	5.000	±	0.524	1.063	0.290	
Mg (mg/dl)	2.068	±	0.266	2.107	±	0.194	-0.534	0.595	
TGs (mg/dl)	119.141	±	26.581	114.000	±	26.796	0.479	0.633	
LDL (mg/dl)	110.764	±	26.451	98.000	±	22.321	1.015	0.313	
HDL (mg/dl)	43.339	±	10.721	44.267	±	8.154	-0.241	0.810	
Cholesterol (mg/dl)	179.329	±	44.251	167.800	±	40.496	0.941	0.349	
EF%	61.324	±	7.475	61.040	±	10.458	0.127	0.899	
Aortic wave pulse velocity (m/s)	1.560	±	0.253	1.387	±	0.275	3.157	0.002*	
Plaques	N	9			8			16.510	<0.001*
	%	10.59			53.33				
IMT (mm)	4.084	±	1.01	6.567	±	1.510	5.150	<0.001*	

Table (4) showed that there was a statistically significant age difference between the two groups (p < 0.001\*), parathyroid hormone level (p = 0.033\*), presence of plaques (p = 0.048\*), and IMT (p < 0.001\*). These factors were found to be increased in patients with AV calcification except PTH showed lower levels. While, there were no significant changes in the duration of hemodialysis, laboratory data, ejection fraction, and aortic PWV.

**Table (4):** Comparison between patients without AV calcification and with AV calcification as regards age, duration of hemodialysis, laboratory data, echocardiography, and carotid duplex findings

	AV calcification						T-Test		
	Without AV calcification 39 patients			With AV calcification 61 patients			T	P-value	
	Mean	±	SD	Mean	±	SD			
Age (years)	34.462	±	13.599	44.590	±	13.771	-3.605	<0.001*	
Duration of HD (years)	6.410	±	4.345	8.246	±	6.665	-1.524	0.131	
Ca (mg/dl)	8.536	±	0.980	8.580	±	0.843	-0.241	0.810	
Ca/po4 product	39.463	±	9.841	37.443	±	9.011	0.675	0.501	
Po4 (mg/dl)	4.644	±	1.110	4.379	±	1.071	0.773	0.441	
PTH (pg/ml)	714.103	±	173.561	494.869	±	11.325	2.165	0.033*	
Hb (g/dl)	9.774	±	1.839	9.910	±	1.435	-0.412	0.681	
Na (mEq/L)	136.513	±	3.892	135.967	±	3.497	0.728	0.468	
K (mEq/L)	5.328	±	0.832	5.108	±	0.716	1.406	0.163	
Mg (mg/dl)	2.072	±	0.271	2.075	±	0.248	-0.069	0.946	
TGs (mg/dl)	122.872	±	29.411	115.492	±	27.321	0.943	0.348	
LDL (mg/dl)	107.164	±	26.021	109.926	±	27.112	-0.298	0.766	
HDL (mg/dl)	44.508	±	10.670	42.820	±	10.495	0.600	0.550	
Cholesterol (mg/dl)	179.615	±	31.587	176.311	±	35.306	0.367	0.714	
EF%	61.723	±	6.651	60.999	±	8.691	0.444	0.658	
Aortic wave pulse velocity (m/s)	1.356	±	0.253	1.418	±	0.276	-1.124	0.264	
Plaques	N	3			14			3.925	0.048*
	%	7.69			22.95				
IMT (mm)	3.546	±	0.781	5.038	±	1.123	-4.050	<0.001*	

There was a statistically significant difference between the two groups in terms of several factors. The factors included serum triglycerides ( $p = 0.050^*$ ), EF ( $p = 0.040^*$ ), aortic PWV ( $p = 0.012^*$ ), and IMT ( $p < 0.001$ ). Patients with carotid plaques had higher levels of aortic PWV and IMT, while their EF and triglycerides were lower compared to the other group (Table 5).

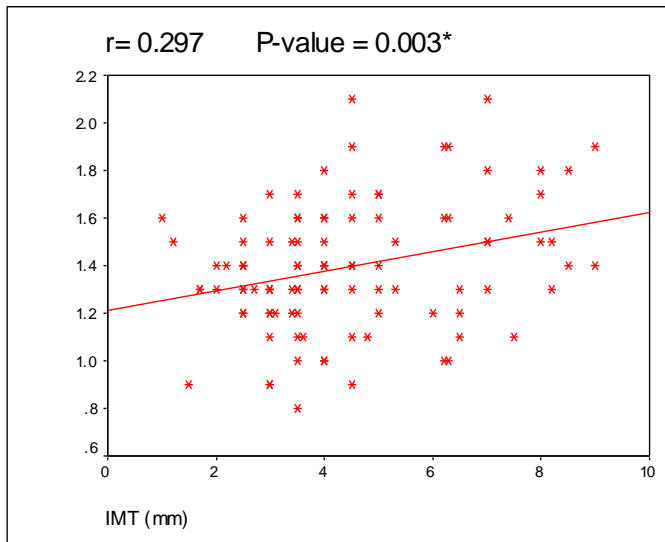
**Table (5):** Comparison between patients without and with carotid plaques as regards age, duration of hemodialysis, laboratory data, echocardiography, and carotid duplex findings

	Carotid Plaques		T-Test	
	Without carotid plaques 83 patients	With carotid plaques 17 patients	T	P-value
	Mean ± SD	Mean ± SD		
Age (years)	40.241 ± 14.441	42.588 ± 15.141	-0.606	0.546
Duration of HD (years)	7.265 ± 5.996	8.824 ± 5.480	-0.990	0.325
Ca (mg/dl)	8.570 ± 0.875	8.529 ± 1.012	0.169	0.866
Ca/po4 product	38.619 ± 9.341	36.335 ± 8.889	0.587	0.558
Po4 (mg/dl)	4.529 ± 1.110	4.253 ± 1.040	0.619	0.537
PTH (pg/ml)	573.518 ± 33.446	613.824 ± 39.442	-0.300	0.765
Hb (g/dl)	9.805 ± 1.537	10.112 ± 1.895	-0.720	0.473
Na (mEq/L)	136.169 ± 3.741	136.235 ± 3.251	-0.068	0.946
K (mEq/L)	5.195 ± 0.785	5.188 ± 0.695	0.034	0.973
Mg (mg/dl)	2.075 ± 0.261	2.071 ± 0.237	0.060	0.952
Triglycerides (mg/dl)	121.747 ± 29.785	101.882 ± 25.067	1.985	0.050*
LDL (mg/dl)	110.004 ± 16.981	103.212 ± 24.889	0.566	0.573
HDL (mg/dl)	43.395 ± 10.240	43.882 ± 10.925	-0.133	0.894
Cholesterol (mg/dl)	179.867 ± 42.327	166.529 ± 40.012	1.148	0.254
EF%	62.016 ± 7.842	57.696 ± 7.581	2.080	0.040*
Aortic wave pulse velocity (m/s)	1.364 ± 0.256	1.541 ± 0.283	-2.556	0.012*
IMT (mm)	3.801 ± 0.931	7.653 ± 0.814	-11.331	<0.001*

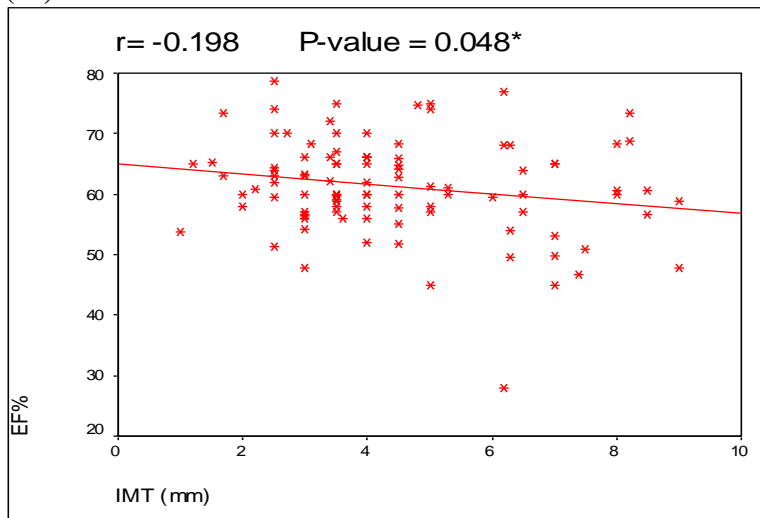
There was a substantial positive association between IMT and age ( $p = 0.022^*$ ), aortic PWV ( $p = 0.003^*$ ), and a significant negative correlation between IMT and ejection fraction (Table 6 and Figures 1 & 2).

**Table (6):** Correlation between intimal medial thickness and age, duration of hemodialysis, laboratory data, echocardiography, and carotid duplex findings

	IMT (mm)	
	r	P-value
Age (years)	0.229	0.022*
Duration of HD (years)	0.035	0.730
Ca (mg/dl)	0.013	0.894
Ca/po4 product	-0.017	0.870
Po4 (mg/dl)	-0.013	0.900
PTH (pg/ml)	0.041	0.688
Hb (g/dl)	0.111	0.273
Na (mEq/L)	0.013	0.896
K (mEq/L)	0.015	0.885
Mg (mg/dl)	0.099	0.327
TGs (mg/dl)	-0.169	0.092
LDL (mg/dl)	-0.043	0.667
HDL (mg/dl)	0.062	0.541
Cholesterol (mg/dl)	-0.055	0.586
EF%	-0.198	0.048*
Aortic wave pulse velocity (m/s)	0.297	0.003*



**Figure (11):** Correlation between intimal medial thickness and aortic wave pulse velocity.



**Figure (2):** The correlation between intimal medial thickness and ejection fraction.

Table (7) revealed that there was a statistically significant positive connection between aortic PWV and phosphorus levels ( $p = 0.038^*$ ). Furthermore, a statistically significant weak positive connection was identified between aortic PWV and potassium levels ( $p = 0.040^*$ ). There was also a statistically significant negative connection between aortic PWV and hemoglobin levels ( $p = 0.001^*$ ).

**Table (7):** Correlation between aortic wave pulse velocity and age, duration of hemodialysis, laboratory data, and ejection fraction

	Aortic wave pulse velocity (m/s)	
	r	P-value
Age (years)	-0.101	0.315
Duration of HD (years)	-0.141	0.162
Ca (mg/dl)	-0.082	0.418
Ca/po4 product	0.175	0.081
Po4 (mg/dl)	0.208	0.038*
PTH (pg/ml)	0.088	0.382
Hb (g/dl)	-0.330	0.001*
Na(mEq/L)	0.017	0.870
K (mEq/L)	0.205	0.040*
Mg (mg/dl)	0.045	0.658
TGs (mg/dl)	-0.026	0.797
LDL (mg/dl)	-0.130	0.197
HDL (mg/dl)	-0.066	0.512
Cholesterol (mg/dl)	-0.173	0.085
EF%	-0.016	0.874

## DISCUSSION

The current study assessed the incidence of vascular and valvular calcifications in hemodialysis patients. The study involved 100 patients who were receiving hemodialysis treatment. Their mean age was 40.6 years. Out of these, 55% were males. The leading causes of kidney failure among the patients were hypertensive nephropathy (30 patients) and diabetic kidney disease (23 patients). The mean EF was 61.281 in the studied population, with a mean carotid IMT of 4.456 mm and a mean aortic wave pulse velocity of 1.394 m/s. Among the patients, 15% had MV calcification, 61% had AV calcification, and 17% had carotid plaques. In concordance with our study, 842 hemodialysis patients in Qatar were investigated to ascertain the risk factors and prevalence of VC. The patients were 61.8% males and had a mean age of 59.8 ± 15.3 years. The two most prevalent comorbidities were diabetes and hypertension. However, the study found that MV calcifications were the most prevalent type of calcification, present in 55.5% of patients, followed by vascular calcification in other arterial vessels and aortic calcification<sup>(9)</sup>.

A recent study by **Ikee et al.**<sup>(10)</sup> investigated the incidence of valvular calcifications in hemodialysis patients and their connection to clinical and analytical markers. The results showed that 77.4% of patients had calcification of the aortic valve, while 51.3% had calcification of the MV. Additionally, 44.3% of patients had calcification of both valves. Furthermore, the study found that those with calcification of one valve had significantly higher carotid IMT than those without.

Calcification in both the aorta and MVs in CKD patients, including hemodialysis patients, has been recognized as a sign of systemic atherosclerosis<sup>(11)</sup>. The current study found that patients with and without MV calcification differed significantly in terms of aortic PWV ( $P = 0.002$ ), carotid plaques ( $P < 0.001$ ), and IMT ( $P < 0.001$ ). However, there were no statistically significant differences found in terms of age, length of hemodialysis, or laboratory data. In agreement with our study, A pilot study<sup>(12)</sup> was conducted to investigate the valvular calcification and carotid artery intima-media thickness (CIMT) in asymptomatic HD patients and contrasted them with healthy individuals. The purpose of the study was to determine the risk variables connected to atherosclerosis. The study findings revealed that CIMT and valvular calcifications were more pronounced in HD patients, indicating a higher risk of atherosclerotic development<sup>(12)</sup>. A cross-sectional study by **Leskinen et al.**<sup>(11)</sup> was conducted on a total of 135 CKD patients, including hemodialysis patients, to examine the connection between valvular calcification, intimal arterial disease findings, and calcified carotid plaques. A control group of 58 participants was also evaluated. The study found a strong association between these conditions. The prevalence of mitral annular calcification in dialysis patients was found to be 31%.

Among patients with valvular calcification, 65% had calcified plaques, compared to only 26% in patients without valvular calcification. This difference was statistically significant ( $p = 0.001$ ).

Our study showed that patients with AV calcifications had a mean IMT of 5.038 mm and a higher percentage (22.95%) of carotid plaques, with a mean age of 44.5 years and lower parathyroid hormone levels (mean 494 pg/ml) compared to the non-aortic calcification group. But, regarding the length of hemodialysis, laboratory data, and other Echocardiography results, there was no statistically significant difference. A recent study by **Arita et al.**<sup>(13)</sup> was conducted on 749 patients, which included an evaluation of AV calcification using echocardiography. Out of all the patients, CKD stages 1–2, 3, 4, and 5 were assigned to 127 (17.0%), 221 (29.5%), 237 (31.6%), and 164 (21.9%) of them, respectively. Additionally, carotid artery abnormalities, such as carotid artery plaque (CAP), were searched for in the research. A substantial correlation was found between AVC and the existence of CAP. Moreover, a substantially increased incidence of AVC was seen in individuals with CAP and greater carotid IMT. Unlike our research, the calcium x phosphate product was revealed to be a major risk factor for AVC in individuals receiving dialysis.

Additionally, the study of **Guerraty et al.**<sup>(14)</sup> discovered that PTH levels, serum phosphorus, and calcium levels did not correlate with AVC on its own. These discrepancies may be attributed to the fact that the effect of impaired mineral metabolism on the emergence of AVC is still up for discussion, and more investigation is required to elucidate the relationship between AVC and impaired mineral metabolism.

A multicenter observational study by **Martínez et al.**<sup>(15)</sup> was carried out during a two-year period on individuals who had CKD stages 3 to 5 receiving dialysis. According to the study, there was a higher incidence of aortic and mitral calcification in these patients (43.1% and 31% respectively). Additionally, it was shown that the total carotid plaque area, phosphorus levels, and age were all positively correlated with AV calcification. It was shown that older patients and those with higher Ca x P products had more calcification in MV cases. Because of the hydroxyapatite crystal deposition, this product has been previously recognized as a risk factor for vascular calcification. This phenomenon might be caused by mineral accumulation in the arterial tunica medium, especially in the lower limbs, and alterations in Ca and P metabolism that lead to arterial stiffness. Moreover, this deposit happens at the valve level. The contrast to our study could be explained that it's an observational study with no follow-up done in imaging.

Our study revealed that patients with carotid plaques had higher levels of aortic PWV (mean 1.54 m/s) and IMT (mean 7.653 mm), while their EF (mean 57.6%) and triglycerides (mean 101.8 mg/dl) were significantly lower compared to non-carotid plaques

group. In agreement with our result, a study by **Fagundes et al.** <sup>(16)</sup> on individuals with DM, dyslipidemia, pre-hypertension, or hypertension investigated the connection between PWV and indicators of structural alterations in the carotid arteries and left ventricle. The results showed that patients with carotid plaque had a significantly higher PWV with a p-value of less than 0.0001\*.

In a study by **Benedetto et al.** <sup>(17)</sup> on 135 patients with ESRD, the progression of atherosclerosis with carotid ultrasound was monitored. The study found that the pace at which new plaque developed was a reliable indicator of cardiovascular events on its own. Even after controlling for baseline plaque load and several possible confounding variables, this link persisted. The study also confirmed that a high baseline IMT was predictive of a higher rate of new plaque formation. In a study by **Hojs** <sup>(18)</sup>, compared 28 randomly chosen hemodialysis patients to 28 age- and sex-matched normal controls, it was discovered that IMT at all locations was directly connected with the number of plaques in hemodialysis patients. The study discovered a substantial correlation between IMT and the number of plaques in the common carotid arteries, the area of bifurcation, and the proximal portion of the internal carotid arteries ( $r = 0.629$ ,  $p < 0.001$ ;  $r = 0.655$ ,  $p < 0.001$ ;  $r = 0.716$ ,  $p < 0.001$  respectively).

**Morteza et al.** <sup>(19)</sup> studied the potential link between 61 hemodialysis patients' carotid and femoral plaques and left ventricular hypertrophy and ejection fraction. There was a linear inverse association between the plaque score and the percentage of left ventricular ejection fraction ( $r = -0.404$ ,  $p = 0.001$ ), which is in concordance with our results. Also, the present study showed a substantial positive association between intimal medial thickness and age ( $p = 0.022$ ), aortic wave pulse velocity ( $p = 0.003$ ), and a significant negative correlation between IMT and ejection fraction ( $p = 0.048$ ).

Consistent with the current investigation, a research by **Hojs** <sup>(18)</sup> revealed no correlation between IMT and serum cholesterol, triglycerides, blood pressure, smoking, calcium, phosphorus, product of calcium and phosphorus, and iPTH in patients receiving hemodialysis, nor with the length of dialysis therapy. However, in the common carotid arteries, there was a noteworthy correlation between age and IMT.

Additionally, our study revealed a statistically significant positive correlation between the velocity of the aortic wave pulse and the level of phosphorous ( $p = 0.038$ ) and potassium ( $p = 0.040$ ). Additionally, there was also a statistically significant negative correlation between the velocity of the aortic wave pulse and the level of hemoglobin ( $p = 0.001$ ).

82 CKD patients underwent electron beam computerized tomography (EBCT) for detection of coronary artery calcification and PWV measurements as an indicator of arterial stiffening and they were followed up for 2 years in **Haydar et al.** <sup>(3)</sup>

Study. PWV also positively correlated with patient age, dialysis duration, and time-averaged CRP. However, not with plasma calcium, plasma phosphate, or calcium-phosphorus ion product levels that are time-averaged. The research showed that coronary artery calcification and PWV had a strong connection ( $r = 0.65$ ), even after controlling for variables that may have increased aortic stiffness, such as age and length of dialysis.

## LIMITATIONS

Despite the fact that this is an observational study with a small sample size, it is widely regarded as the most comprehensive and homogenous study of hemodialysis patients to date. The study used multiple diagnostic methods to explore the relative relationship between vascular and valvular calcification and its prevalence in hemodialysis patients.

## CONCLUSIONS

Valvular calcification is a common occurrence in patients undergoing hemodialysis, with AV calcification being more prevalent than MV calcification. AV calcification is more frequent in elderly people and related to secondary hyperparathyroidism. In hemodialysis patients with valvular calcifications, there was an increased prevalence of carotid intimal thickness. This increase in carotid intimal thickness was especially significant in hemodialysis patients with reduced ejection fraction. Aortic wave pulse velocity was associated with increased carotid intimal thickness and predicted arterial atherosclerosis in hemodialysis patients. Additionally, aortic wave pulse velocity was linked to anemia and hyperphosphatemia in hemodialysis patients.

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## REFERENCES

1. **Toussaint N, Kerr P (2007):** Vascular calcification and arterial stiffness in chronic kidney disease: implications and management. *Nephrology*, 12 (5): 500-9.
2. **Giachelli C (2009):** The emerging role of phosphate in vascular calcification. *Kidney Int.*, 75 (9): 890-7.
3. **Haydar A, Covic A, Colhoun H et al. (2004):** Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients. *Kidney Int.*, 65 (5): 1790-4.
4. **Small A, Kiss D, Giri J et al. (2017):** Biomarkers of Calcific Aortic Valve Disease. *Arterioscler Thromb Vasc Biol.*, 37: 623-32.
5. **Bellasi A, Ferramosca E, Muntner P et al. (2006):** Correlation of simple imaging tests and coronary artery calcium measured by computed tomography in hemodialysis patients *Kidney Int.*, 70: 1623-1628.



6. **London G, Marchais S, Guerin A (2004):** Arterial stiffness and function in end-stage renal disease. *Adv Chronic Kidney Dis.*, 11: 202-209.
7. **Goldsmith D, Ritz E, Covic A (2004):** Vascular calcification: a stiff challenge for the nephrologist: does preventing bone disease cause arterial disease? *Kidney Int.*, 66: 1315-33.
8. **Group KDIGO-MW (2009):** KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl.*, 113: 1-130. doi: 10.1038/ki.2009.188.
9. **Ghonimi T, Hamad A, Fouda T et al. (2014):** Cardiovascular calcification in hemodialysis patients: A Qatar-based prevalence and risk factors study. *Qatar Medical Journal*, 18: 1-10. DOI: <https://doi.org/10.5339/qmj.2014.18>.
10. **Ikee R, Honda K, Oka M et al. (2008):** Association of heart valve calcification with malnutrition-inflammation complex syndrome, beta-microglobulin, and carotid intima media thickness in patients on hemodialysis. *Ther Apher Dia.*, 12 (6): 464-8.
11. **Leskinen Y, Paana T, Saha H et al. (2009):** Valvular calcification and its relationship to atherosclerosis in chronic kidney disease. *J Heart Valve Dis.*, 18: 429-38.
12. **Ardahanli I, Cengizhan M, Celik M et al. (2019):** Carotid Artery Intima-Media Thickness and Heart Valve Calcifications in Hemodialysis Patients with Hyperparathyroidism (A Pilot Study). *Arch Nephrol Urol.*, 2 (2): 052-061.
13. **Arita Y, Nakayama M, Matsukuma Y et al. (2020):** Association of aortic valve calcification with carotid artery lesions and peripheral artery disease in patients with chronic kidney disease: a cross-sectional study. *BMC Nephrol.*, 21 (1): 203. doi: 10.1186/s12882-020-01864-z
14. **Guerraty M, Chai B, Hsu J et al. (2015):** CRIC Study Investigators. Relation of aortic valve calcium to chronic kidney disease (from the chronic renal insufficiency cohort study). *Am J Cardiol.*, 115: 1281-6.
15. **Martínez F L, Sánchez-Alvarez J, de la Tassa C et al. (2021):** Risk factors associated with valvular calcification in patients with chronic kidney disease. Analysis of NEFRONA study. *Nefrologia*, 41 (3): 337-346.
16. **Fagundes R, Vitorino P, Lelis E et al. (2020):** Relationship between Pulse Wave Velocity and Cardiovascular Biomarkers in Patients with Risk Factors. *Arq Bras Cardiol.*, 115 (6): 1125-1132.
17. **Benedetto F, Tripepi G, Mallamaci F et al. (2008):** Rate of atherosclerotic plaque formation predicts cardiovascular events in ESRD. *J Am Soc Nephrol.*, 19 (4): 757-63.
18. **Hojs R (2000):** Carotid intima-media thickness and plaques in hemodialysis patients. *Artif Organs.*, 24 (9): 691-95.
19. **Mowlaie M, Nasri H (2014):** Close association of arterial plaques with left ventricular hypertrophy and ejection fraction in hemodialysis patients. *J Nephropharmacol.*, 3 (1): 9-12.